

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
25 April 2002 (25.04.2002)

PCT

(10) International Publication Number
WO 02/32428 A1

- (31) International Patent Classification⁷: **A61K 31/505**,
A61P 3/06, A61K 31/40
- (21) International Application Number: **PCT/GB01/04525**
- (22) International Filing Date: 12 October 2001 (12.10.2001)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Date: 0003766-3 18 October 2000 (18.10.2000) SE
- (71) Applicant (for all designated States except MG, US): **ASTRAZENECA AB** [SE/SE]; S-151 85 Sodertälje (SE).
- (71) Applicant (for MG only): **ASTRAZENECA UK LIMITED** [GB/GB]; 15 Stanhope Gate, London W1Y 6LN (GB).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **STARKE, Ingemar** [SE/SE]; S-431 83 Mölndal (SE). **ABRAHAMSSON, Bertil** [SE/SE]; S-431 83 Mölndal (SE). **UNGELL, Anna-Leen** [SE/SE]; S-431 83 Mölndal (SE). **LINDQVIST, Ann-Margret** [SE/SE]; S-431 83 Mölndal (SE).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:
- with international search report
 - before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: ORAL FORMULATION COMPRISING AN INHIBITOR COMPOUND OF THE ILEAL BILE TRANSPORT AND AN HMG Co A REDUCTASE INHIBITOR

(57) Abstract: An oral pharmaceutical formulation comprising an inhibitor compound of the ileal bile acid transport (IBAT inhibitor), an HMG Co-A reductase inhibitor and a therapeutically acceptable carrier characterised in that the formulation is designed to deliver the IBAT inhibitor in the ileum and the HMG Co A reductase inhibitor non-specifically into the GI tract. The IBAT inhibitor compound and the HMG Co-A reductase inhibitor can also be administered in combination with a bile acid binder to alleviate possible side effects of therapy with IBAT inhibitor compounds, such as for instance diarrhoea. The bile acid binder may be formulated for colon release.

WO 02/32428

PCT/GB01/04525

- 1 -

ORAL FORMULATION COMPRISING AN INHIBITOR COMPOUND OF THE ILEAL BILE TRANSPORT
AND AN HMG CO-A REDUCTASE INHIBITOR

The present invention relates to a formulation comprising a substance with inhibitory effect on the ileal bile acid transport system (IBAT inhibitor) in association with an HMG Co-
5 A reductase inhibitor wherein the formulation is designed to deliver the IBAT inhibitor into the ileum and the HMG Co-A reductase inhibitor non-specifically into the gastro-intestinal (GI) tract. The invention also relates to manufacturing processes and the use of the dosage form in the treatment of hypercholesterolaemia. A further aspect of the invention is the use of an IBAT inhibitor in association with both a bile acid binder and an HMG Co-A reductase
10 inhibitor by simultaneously, separately or sequentially administration of the three substances, and the use of these substances in the manufacture of such a pharmaceutical dosage form.

It is well known that hyperlipidemic conditions associated with elevated concentrations of total cholesterol and low-density lipoprotein cholesterol are major risk factors for coronary heart disease and particularly atherosclerosis. Interfering with the
15 circulation of bile acids within the lumen of the intestinal tracts is found to reduce the level of cholesterol. Previous established therapies to reduce the concentration of cholesterol involve for instance treatment with an HMG-CoA reductase inhibitor, preferably a statin such as simvastatin and fluvastatin, or treatment with a bile acid binder, such as a resin. Frequently used bile acid binders are for instance cholestyramine and cholestipol.

20 One recently proposed therapy involves the treatment with substances with inhibiting effect on the ileal bile acid transport system. Re-absorption of bile acid from the gastro-intestinal tract is a normal physiological process, which mainly takes place in the ileum by an active transport mechanism called ileal bile acid transport. IBAT inhibitors can be used in the treatment of hypercholesterolaemia. See for instance "Interaction of bile acids and cholesterol
25 with nonsystemic agents having hypocholesterolemic properties", Biochemica et Biophysica Acta, 1210 (1994) 255- 287. Thus, suitable compounds having such inhibitory IBAT activity are also useful in the treatment of hyperlipidaemic conditions.

Several chemical compounds possessing such IBAT activity have recently been described, see for instance hypolipidaemic benzothiazepine compounds described in
30 International Patent Application, Publication No. WO 93/16055 and WO 96/16051; condensed 1,4-thiazepines described in International Patent Application, Publication No. WO 94/18183; different heterocyclic compounds described in International Patent Application, Publication No. WO 94/18184; and 1,4-benzothiazepine-1,1-dioxides described in

WO 02/32428

PCT/CB01/04525

- 2 -

International Patent Application, Publication No. WO 96/05188, all of which are hereby incorporated by reference.

Further, especially suitable compounds for the present invention are for instance benzothiazepines with IBAT activity described in International Patent Application, Publication No. WO 96/08484; bile acid resorption inhibitors described in International Patent Application, Publication No. WO 97/33882, WO 98/07449 and WO 98/03818, and in European Patent Application, Publication No. EP-A-0864582, EP-A-0489423, EP-A-0549967, EP-A-0573848, EP-A-0624593, EP-A-0624594, EP-A-0624595, and EP-A-0624596, all of which are hereby incorporated by reference. Further compounds of interest can be found in International Patent Application, Publication No. WO 99/32478, WO 99/644/99 and WO 00/01687, all of which are hereby incorporated by reference.

It is proposed that these types of compounds can be administered by any conventional means available for use in conjunction with pharmaceuticals. For instance, the dosage forms can be a daily dose which is administered once a day or being divided to be administered several times a day, or alternative in a sustained release form. Suitable dosage forms are intended for oral administration.

All benzothiazepines, however, will not be effective as IBAT inhibitor compounds. Thus, diltiazem, which is a 1,5-benzothiazepine, is a calcium blocker with coronary vasodilating activity (see The Merck Index, Merck & Co, Inc., 12th ed., 1996, p. 541). With respect to inhibition of IBAT, diltiazem has no activity.

In general, pharmaceutical drug substances will be absorbed in the upper small intestine, and therefore only a small amount will reach ileum when administered in a conventional oral dosage form. Irrespective of the construction of the pharmaceutical dosage form, ideally the formulation should provide delivery of the active compound, e.g. IBAT inhibitor, into the compound's site of action in the body, for example in the ileum. The above prior art documents discuss in general terms suitable pharmaceutical dosage forms for the described IBAT inhibitor compounds. However, none of the documents describe a specific way to obtain a release of the active substance directly to or close to the site of action.

Contact between the active drug and the site of action can be established in different ways. The present application describes a new pharmaceutical dosage form which reduces and minimises absorption, metabolism and dilution in the luminal content of the IBAT inhibitor in the body before it reaches the site of action.

WO 02/32428

PCT/GB01/04525

- 3 -

It has been proposed that after absorption over the gastro-intestinal membrane, an IBAT inhibitor could interact with transport systems similar to IBAT for instance the corresponding transport system in the liver (LBAT) or it could provide other non-specific systemic effects which could lead to undesirable pharmacological or even toxicological effects. This could severely limit the clinical usefulness of IBAT inhibitors especially in the treatment of hypercholesterolaemia, i.e. conditions associated with elevated concentrations of total cholesterol and low-density lipoprotein cholesterol.

The inhibition of the re-absorption of bile acids from the small intestine performed by an effective IBAT inhibitor may lead to increased levels of bile acids in the lower parts (colon) of the gastro-intestinal tract. Such an increase of bile acid concentrations in the distal regions could potentially generate diarrhoea and discomfort to the patient. The present invention provides a new approach to minimise the concentration of free bile acids in the colon and thereby reduce the potential risk of adverse events by co-administration of a bile acid binder together with the IBAT inhibitor. However, the combination of an IBAT inhibitor and a bile acid binder have previously been proposed in the above patent applications describing new IBAT inhibitor compounds. The purpose of such previously described combinations have been to enhance the cholesterol lowering efficacy of the therapy, and there is no hint that such a combination could be used to minimise a potential risk for diarrhoea connected with IBAT inhibitor therapy.

The aim of the present invention is to reduce the problem with undesirable side effects of IBAT inhibitor compounds by providing a pharmaceutical formulation, which reduces the systemic drug exposure while maintaining or enhancing the cholesterol lowering effect of the drug. Such undesirable systemic effects put a load on other organs, e.g. liver and kidneys. Thus, the present dosage form provides a reduced, i.e. minimum absorption, metabolism and dilution in the luminal content of the IBAT inhibitor by a specific targeting to the site of action. The release is directed specifically to the site of action which reduces or even might avoid toxicological effects of the drug. The formulation is intended to be orally administered and pass through the upper part of the small intestine with a minimum release of the IBAT inhibitor before it reaches the distal jejunum or proximal ileum.

The present invention provides such a dosage form, which delivers the main part of the dose to the site of action, i.e. in the distal jejunum, in the proximal ileum or in the distal ileum. The release of the drug is thereby reduced or minimised to more proximal parts, the duodenum and jejunum, where drug absorption in general is most efficient. Thus, the release

WO 02/32428

PCT/GB01/04525

- 4 -

of the drug should preferably start in the distal jejunum or proximal ileum, or the entire dose should be delivered directly to the ileum.

Preferably, the formulation is an orally administered formulation, such as a delayed release formulation, which starts to release the main part of the drug in the distal jejunum or in the proximal ileum. The oral formulation might also provide protection of the drug from the acid environment in the stomach by an enteric coating. Such an enteric coating also protects the gastric mucosa from drug exposure and thereby minimises irritation or even damages of the gastric mucosa potentially caused by aggressive drug exposure.

An additional aim of the present invention is to provide a combination for simultaneous, separate or sequential administration which combination comprises an IBAT inhibitor, and HMG Co-A reductase inhibitor and a bile acid binder. Such a combination will protect the patient from any possible side effect caused by excess of bile acids in the colon, such as diarrhoea. If the transport of bile acids is blocked by an IBAT inhibitor the bile acids might be deposited in the colon and induce a secretory diarrhoea - by irritation and inflammation - as a undesired side effect caused by the treatment with an IBAT inhibitor.

Another aspect of the provided combination therapy is that the bile acid binder, for instance a resin such as cholestyramine or cholestipol, could preferably be administered in a dosage form with colon release of the bile acid binder. A colon release formulation will provide protection of the bile acid binder to the luminal contents in the more proximal parts of the intestine, where the bile acid concentrations are high. Such a formulation will prevent binding of bile acids to the bile acid binder before the formulation reaches the colon. Thereby, maximal bile acid binding capacity will be obtained in the colon and any possible gastrointestinal side effects, such as diarrhoea, may be avoided. Thus, any additional amount of bile acid presented in the colon due to the treatment with the IBAT inhibitor compound, would be bound to a bile acid binder, which the bile acid binder is preferably delivered in the colon, thereby any possible side effects such as diarrhoea is avoided.

IBAT inhibitor compounds

Active ingredients suitable as IBAT inhibitor compounds in the present invention are those exhibiting activity when screening for IBAT inhibiting properties. Suitable examples of such compounds can be found in the references cited on page 2 of the present application.

Active ingredients particularly suitable as IBAT inhibitor compounds in the present invention include benzothiazepines, and more particularly 1,4-benzothiazepines and 1,5-benzothiazepines exhibiting activity when screening for IBAT inhibiting properties. Of these,

WO 02/32428

PCT/GB01/04525

- 5 -

compounds with an oxidised sulphur group, particularly a sulphone group, in the 7 membered ring are preferred. Furthermore, the presence of an amine group in the 7 membered ring is preferred.

HMG Co-A reductase inhibitor compounds

- 5 Active ingredients suitable as HMG Co-A reductase inhibitors are statins well known in the art. Particular statins are fluvastatin, lovastatin, pravastatin, simvastatin, atorvastatin, cerivastatin, bervastatin, dalvastatin, mevastatin and (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulphonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid or pharmaceutically acceptable salts thereof. A particular statin is atorvastatin or a
- 10 pharmaceutically acceptable salt thereof. A further particular statin is (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulphonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof.

- A suitable pharmaceutically acceptable salt is, for example, an acid-addition salt of a compound of the invention which is sufficiently basic, for example, an acid-addition salt with,
- 15 for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric or maleic acid. In addition a suitable pharmaceutically acceptable salt of a compound of the invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a
- 20 physiologically-acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine. Preferably a pharmaceutically acceptable salt is the calcium salt.

Pharmaceutical formulations

- According to one aspect of the invention, an orally administered pharmaceutical
- 25 formulation of an IBAT inhibitor and an HMG Co-A reductase inhibitor is provided, which formulation releases HMG Co-A reductase inhibitor non-specifically into the GI tract and almost the entire dose of the IBAT inhibitor compound in the distal jejunum, in the proximal ileum, or deliver the dose directly to the ileum. Such a formulation will minimise release of the IBAT inhibitor in the upper part of the small intestine, i.e. above distal jejunum whereas
- 30 the HMG CoA reductase inhibitor will not be targeted to any specific site in the gastrointestinal tract.

The HMG CoA reductase inhibitor will be delivered in a form that is not intended for targeting to any specific site in the gastro-intestinal tract at a rate that makes the complete

WO 02/32428

PCT/GB01/04525

- 6 -

dose available immediately after intake or during a prolonged period of time. Conventional excipients and techniques used for manufacturing of tablets, capsules or beads can be employed.

Optimal IBAT inhibitor release and binding to the IBAT in the ileum can for instance
5 be obtained by a delayed release formulation, such as a formulation with a specified lagtime. More specifically, less than 30 % of the drug could be released during the time the formulation spends in the stomach and in the proximal small intestine, i.e. during the passage of the upper part of the small intestine.

Thus, according to a second aspect, the present invention provides a pharmaceutical
10 formulation with a delayed release of the IBAT by a controlled lagtime. The part of the formulation containing the IBAT inhibitor shall pass the duodenum and jejunum with a minimum release of the active IBAT inhibitor, and thereby increasing the dose available for binding to the site of action in the ileum and thereby increasing the inhibition of the ileal bile acid transport system. Preferably, the lagtime period is about 0.5 - 2 hours calculated from
15 emptying from the stomach, and more than 70 % of the dose should be released approximately during the next 0.5 - 2.0 hours, i.e. after the lagtime period. More preferably, the dose should be released during the first hour after the lagtime period.

Dosage forms with a controlled lagtime can be constructed in different ways for instance as described in the following.

20 A controlled lagtime can be triggered by pH changes, redox potential differences or luminal metabolic changes in the gastro-intestinal tract as described in Aliment Pharmacol Ther 1997, 11 (suppl 3): 109-115. Such a controlled lagtime could be obtained for instance by a programmed disintegration of the formulation due to erosion, dissolution or in general by components present in the formulation interacting with the environment in the gastro-
25 intestinal tract. Preferably, the drug release from the dosage form could be triggered by the pH variation between jejunum and ileum.

Alternatively, the drug release from the dosage form can be chronographic controlled to obtain the above specified time limits, such as for instance described in the European Patent Application, Publication No. EP-A-0384642.

30 When the formulation reaches the distal jejunum or the ileum, the drug release should preferably be either immediately, with a sustained release or be based on a combination of such release principles. The duration of the drug release for a sustained release formulation should preferably not exceed 2 hours.

WO 02/32428

PCT/GB01/04525

- 7 -

According to a third aspect of the invention, a sustained release formulation can be constructed by any known principle, such as eroding or non-eroding matrices, membrane-coating layers or by diffusion or osmotically driven drug release. Suitable techniques for the construction of such formulations are for instance described in M. B. Aulton, *Pharmaceutics, The science of dosage form design*. (1988).

An additional aspect of the invention is to combine an IBAT inhibitor, an HMG Co-A reductase inhibitor and a bile acid binder thereby avoiding a possible risk of excess of bile acids in colon caused by the inhibition of the ileal bile acid transport system. An excess of bile acids in the visceral contents may cause diarrhoea. Thus, the present invention also provides a treatment of a possible side effect such as diarrhoea in patients during therapy comprising IBAT inhibitors.

An HMG CoA-reductase inhibitor will by its action decrease the endogenous cholesterol available for the bile acid synthesis and have an additive effect in combination with an IBAT-inhibitor on lipid lowering.

Suitable bile acid binders for such a combination therapy are resins, such as cholestyramine and cholestipol. One advantage is that the dose of bile acid binder might be kept lower than the therapeutic dose for treatment of cholesterolaemia in single treatment comprising solely a bile acid binder. By a low dose of bile acid binder any possible side effects caused by poor tolerance of the patient to the therapeutic dose could also be avoided.

A further aspect in connection with such a combination therapy is that the bile acid binder could be administered in a dosage form with colon release, i.e. delivery of the active dose of bile acid binder in the colon. A possible risk of receiving an excess of bile acid in the colon by treatment with an IBAT inhibitor could be avoided by co-administration of a bile acid binder with colon release. Thus, any excess of bile acid in the colon, with a possible risk to cause diarrhoea, will be bound into a resin. The dose of the bile acid binder could be kept low due to an effective use of the dose by such a colon release. The colon delivery of the bile acid binder can be obtained by a formulation comprising a core containing the bile acid binder and optionally pharmaceutically acceptable excipients, and a coating of said core with a delayed release membrane adapted for colonic delivery. Technologies to obtain such a delivery of drugs to the colon are for example described in *Drug Development and Industrial Pharmacy* 1997, 23: 893-913.

Further general aspects of the invention are that the formulations can be solid, semi-solid or liquid formulations. In a solid formulation, the carrier can be monolithic, such as

WO 02/32428

PCT/GB01/04525

- 8 -

tablets or capsules. One preferred monolithic formulation is a coated tablet, a capsule comprising small, coated units or a multiple unit tablet comprising a multitude of small coated units. Semi-solid or liquid formulations can be administered in capsules suitable for such vehicles. The most preferred formulation is an oral formulation such as a tablet or a capsule comprising coated small units or pellets. The formulation or dosage form may contain from 0.05% to 95% of the active compound in admixture with a pharmaceutically acceptable carrier, or pharmaceutically acceptable excipients.

Preparation of core material containing an IBAT inhibitor

The core material for the units, i.e. the tablets or the individual pellets can be constituted according to different principles. The core material may be homogenous or heterogeneous. The core containing the active principle may be differently formulated such as monolithic tablets, capsules, granules, pellets, other particles or crystals.

With a homogenous core material is meant, that it has a homogenous distribution of active substance throughout the core material.

The active substance, i.e. the IBAT inhibitor, is optionally mixed with further components to obtain preferred handling and processing properties and a suitable concentration of the active substance in the final mixture. Such components can be binders, surfactants, lubricants, glidants, fillers, additives or other pharmaceutically acceptable ingredients, alone or in mixtures.

Said core material may be produced either by direct compression of the mixed ingredients, or by granulation of the ingredients followed by compression of the granulated material. In direct compression, the ingredients are mixed and compressed by using ordinary tableting equipment.

For the granulation there are numerous alternatives of granulating procedures mentioned in the literature, dry methods like roller compaction (Chilsonator) and wet methods utilizing granulating solutions with and without the addition of binders. A variant of the wet methods is to make a spray-granulation in a fluid bed.

For the wet granulating methods, either organic solvents, aqueous solutions or pure water may be utilized to prepare the granulating solutions. Due to environmental considerations pure water is preferred, if it is possible due to the composition of the mixture.

Homogenous core particles can also be prepared by techniques such as dry or wet milling, freeze milling, air-jet micronisation, spray drying, spray chilling, controlled

WO 02/32428

PCT/GB01/04525

- 9 -

crystallisation, supercritical crystallisation, emulsion solvent evaporation and emulsion solvent extraction.

The core material may also be produced by extrusion/spheronization, balling or compression, utilizing different process equipments.

- 5 The size of the formulated core materials is approximately between 2 and 14 mm, preferably between 3 and 9 mm for a tablet preparation, and between 0.001 and 4 mm, preferably between 0.001 and 2 mm for a pellet preparation.

The manufactured core material may be further layered with additional ingredients comprising the active substance and/or be used for further processing.

- 10 Alternatively, the core material may be heterogeneous with an inner zone, for instance a seed or sphere, not containing the active substance. A layer comprising the active substance, and optionally pharmaceutically acceptable excipients, surrounds this seed or sphere.

- The seed or sphere may be soluble or insoluble. Optionally, the seed or sphere (inner zone) may be coated with an inert layer to prepare a smooth surface before the layer
15 containing active substance is applied onto the seed/sphere.

- Insoluble seeds/spheres may comprise different oxides, celluloses, organic polymers and other materials, alone or in mixtures. Water-soluble seeds/spheres may comprise different inorganic salts, sugars and other materials, alone or in mixtures. The size of the seeds may vary between approximately 0.1 and 2 mm. The seeds layered with the matrix containing the
20 active substance are produced either by powder or solution/suspension layering using for instance granulating or spray coating/layering equipment.

Processes for application of delayed release membranes of IBAT inhibitor beads

- Delayed release membrane can be applied to the core material, being a monolithic tablet, multiple units or a hard or soft gelatine capsule, by coating or layering procedures in
25 suitable equipment such as coating pans, coating granulators or in a fluidized bed apparatus using water and/or organic solvents for the coating process. Also powder-coating principles may be applied. Another possibility is to apply the coating by microencapsulation techniques such as coacervation, emulsification with subsequent removal of the solvent by extraction or evaporation, ionotropic gelation or congealing.

- 30 Such delayed release membranes may be applied on core material comprising the IBAT inhibitor for delivery to the distal small intestine and optionally also be applied to the bile acid binder for delivery to the colon.

Pharmaceutical additives

WO 02/32428

PCT/GB01/04525

- 10 -

Delayed release coatings may be obtained by one or more, separately or in compatible combinations of pharmaceutically acceptable ingredients, in amounts carefully titrated to reach the intended release properties. As coating layer, the following pH sensitive polymers can be applied; e.g. methacrylic acid copolymers, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, carboxymethyl ethyl-cellulose, shellac or other suitable enteric coating layer polymer(s). The coating layer may also be composed of film-forming polymers being sensitive to other luminal components than pH, such as bacterial degradation or a component that has such a sensitivity when it is mixed with another film-forming polymer. Examples of such components providing delayed release to the intended regions are; polymers comprising azo bond(s), polysaccharides such as pectin and its salts, galactomannans, amylose and chondroitin, disulphide polymers and glycosides.

The delayed release coating or an additional coating of the formulation may contain other film-forming polymers being non-sensitive to the luminal conditions for technical reasons or chronographic control of the drug release. Materials to be used for such purposes includes, but are not limited to; sugar, polyethylene glycol, polyvinylpyrrolidone, poly-vinyl alcohol, polyvinyl acetate, hydroxypropyl cellulose, methylcellulose, ethylcellulose, hydroxypropyl methylcellulose, carboxymethylcellulose sodium and others, used alone or in mixtures.

Additives such as dispersants, colorants, pigments, additional polymers e.g. poly(ethylacrylat, methylmethacrylat), anti-tacking and anti-foaming agents may also be included into the coating layer. Other compounds may be added to increase film thickness and to decrease diffusion of acidic gastric juices into the core material.

The coating layers may also contain pharmaceutically acceptable plasticizers to obtain desired mechanical properties. Such plasticizers are for instance, but not restricted to, triacetin, citric acid esters, phthalic acid esters, dibutyl sebacate, cetyl alcohol, polyethylene glycols, glycerol monoesters, polysorbates or other plasticizers and mixtures thereof. The amount of plasticizer is preferably optimised for each formula, in relation to the selected polymer(s), selected plasticizer(s) and the applied amount of said polymer(s).

In preparation of tablets, either as monolithic drug containing cores for subsequent coating with a delayed release membrane or as a matrix for coated multiple units, additional ingredients may be needed to obtain suitable technical properties such as binders, disintegrants, bulk agents, glidants, lubricants, and coatings agents without effects on the drug

WO 02/32428

PCT/GB01/04525

- 11 -

release such as water soluble polymers, anti-tacking agents, colourants, pigments and waxes. Ingredients well known for such usage are for example described in "Handbook of pharmaceutical excipients", 2nd edition, 1994, Pharmaceutical Press, London.

Preparation of final dosage forms

- 5 A HMG CoA reductase inhibitor and a coated units containing an IBAT inhibitor may be filled into hard gelatine capsules or compressed into tablets after mixing with appropriate excipients, such as fillers, binders, disintegrants, lubricants and other pharmaceutically acceptable additives. A compressed tablet is optionally covered with film-forming agents to obtain a smooth surface of the tablet and further enhance the mechanical stability of the tablet
- 10 during packaging and transport. Such a tablet coat, which may be applied on a multiple unit tablet or a conventional tablet, may further comprise additives like anti-tacking agents, colourants and pigments or other additives to improve the tablet appearance.

Suitable drugs for the new formulations are IBAT inhibitors such as described in the above-discussed documents, are hereby incorporated by references.

- 15 The IBAT inhibitor compound could alternatively be a low permeability drug as defined in the Biopharmaceutical Classification System proposed by FDA.

- A combination therapy according to the invention should preferably comprise simultaneously, separately or sequentially administration of an IBAT inhibitor compound, an HMG Co-A reductase inhibitor and a bile acid binder. The IBAT inhibitor could preferably be
- 20 formulated for ileum delivery, the HMG Co-A reductase inhibitor could preferably be formulated for proximal intestine delivery and the bile acid binder could preferably be formulation for colon release.

Medical and pharmaceutical use of the invention

- The pharmaceutical formulations according to the present invention can be used in the
- 25 treatment of hypercholesterolaemia. A suitable unit dose will vary with respect to the patients body weight, condition and disease severity. The dose will also depend on if it is to be used for prophylaxis or in the treatment of severe conditions, as well as the route of administration. The daily dose can be administered as a single dose or divided into two or more unit doses. An orally administered daily dose of an IBAT inhibitor is preferably within 0.1 - 1,000 mg,
- 30 more preferable 1 - 100 mg. An orally administered daily dose of an HMG Co-A reductase inhibitor is preferably within 0.1-160mg.

A pharmaceutical formulation according to the present invention with a targeted delivery in the gastro intestinal tract provides a reduced systemic exposure, as can be

WO 02/32428

PCT/GB01/04525

- 12 -

measured by the area under the drug plasma concentration versus time curve (AUC), while maintaining or even increasing the therapeutic effect, as e.g. measured by serum cholesterol reduction.

- A combination therapy comprising an IBAT inhibitor, an HMG Co-A reductase inhibitor and a bile acid binder comprises preferably a low daily dose of the bile acid binder, such as less than 5 g of a resin, and more preferably less than 2 g. A dosage form with colon release of the bile acid binder could be constructed by any of the above described principles for delayed release formulations.

- The following contemplated Examples are intended to illustrate, but in no way limit the scope of the invention.

EXAMPLES

Example 1

A formulation having the following composition can be prepared:

| | amount/capsule (mg) |
|---|---------------------|
| IBAT inhibitor (1,5-benzothiazepine) | 10 |
| Non pareil spheres | 500 |
| Ethyl cellulose | 2 |
| Hydroxypropylmethyl cellulose | 10 |
| Eudragit L100-55 | 25 |
| Triethylcitrate | 2.4 |
| HMG Co-A reductase inhibitor ¹ | 5 |
| lactose | 60 |
| Magnesium stearate | 0.5 |
| ¹ (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulphonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid calcium salt | |

- The active drug can be dissolved together with ethyl cellulose and hydroxypropyl cellulose in ethanol 99 %. The mixture can then be sprayed onto the non-pareil spheres in a fluidized bed apparatus. Thereafter, the pellets can be dried and aerated to remove residual ethanol. The Eudragit L100-55 dispersion with addition of triethyl citrate can then be sprayed onto the drug beads in a fluidized bed apparatus. The coated beads can thereafter be dried and sieved.

The HMG CoA reductase inhibitor can be mixed with lactose in a high speed mixer. The powder can thereafter be granulated by addition of water in the mixer. The formed

WO 02/32428

PCT/GB01/04525

- 13 -

granulate may subsequently be dried and sieved. Magnesium stearate can then be added to the sieved granulate in a high speed mixer.

Finally, the coated beads and the granulate can be filled in hard gelatine capsules.

Example 2

- 5 A formulation having the following composition can be prepared:

| | amount/tablet (mg) |
|---|--------------------|
| IBAT inhibitor (1,5-benzothiazepine) | 10 |
| HMG Co-A reductase inhibitor ¹ | 5 |
| Silicon dioxide | 200 |
| 10 Povidone K-25 | 20 |
| Eudragit FS30D | 30 |
| Microcrystalline cellulose | 250 |
| Sodium stearyl fumarate | 5 |

- ¹ (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulphonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid calcium salt
- 15

- The IBAT inhibitor can be suspended in water and sprayed onto silicon dioxide cores of a predefined size in a fluidized bed apparatus. The drug pellets can be dried in an oven at 40° C for 24 h. Thereafter, a layer of Povidone K-25 can be applied on the beads from an ethanolic solution in a fluidized bed apparatus. A final coat of Eudragit FS30D dispersion can be applied thereafter in a fluidized bed. The coated beads can be mixed with a HMG CoA reductase inhibitor, microcrystalline cellulose and sodium stearyl fumarate in a mixer and subsequently compressed to tablets.
- 20

WO 02/32428

PCT/GB01/04525

- 14 -

Claims

What is claimed is:

- 5 1. An oral pharmaceutical formulation comprising an inhibitor compound of the ilea. bile acid transport (IBAT inhibitor) an HMG Co-A reductase inhibitor and a pharmaceutically acceptable carrier, wherein the formulation is designed to deliver the IBAT in the ileum and the HMG Co A reductase inhibitor non-specifically to the GI tract.
- 10 2. The oral pharmaceutical formulation according to claim 1, wherein the formulation is designed to deliver HMG CoA reductase non-specifically into the GI tract and the IBAT inhibitor in the ileum by release in one or more parts of the body selected from the distal jejunum and proximal ileum, and/or directly in the ileum.
- 15 3. The formulation according to claim 1, wherein the carrier is designed to deliver the HMG Co-A reductase inhibitor non-specifically into the GI tract and the IBAT inhibitor in the ileum.
4. The formulation according to claim 1, wherein the carrier is designed to release the
20 HMG CoA reductase non-specifically into the GI tract and the IBAT inhibitor in the distal jejunum and in the proximal ileum.
5. The formulation according to any one of the claims 1 to 4, wherein the carrier is designed to give a minimum release of the IBAT inhibitor in the upper part of the small
25 intestine.
6. The formulation according to any one of claims 1 to 4, wherein the pharmaceutical formulation is a delayed release formulation.
- 30 7. The formulation according to claim 6, wherein the formulation provides a lagtime of about 0.5 - 2 hours after emptying the stomach.

WO 02/32428

PCT/GB01/04525

- 15 -

8. The formulation according to claim 7, wherein the IBAT inhibitor is released during the first hour after the lagtime.

9. The formulation according to claim 6, wherein release of the IBAT inhibitor and the HMG Co-A reductase inhibitor from the delayed release formulation is triggered by the pH differences between the jejunum and ileum.

10. The formulation according to any one of claims 1 to 9, wherein the IBAT inhibitor is a low permeability drug as defined in the Biopharmaceutical Classification System FDA.

10

11. The formulation according to any one of claims 1 to 9, wherein the HMG Co-A reductase inhibitor is atorvastatin or a pharmaceutically acceptable salt thereof.

12. The formulation according to any one of claims 1 to 9, wherein the HMG Co-A reductase inhibitor is (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulphonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof.

15

13. The use of a pharmaceutical formulation comprising an IBAT inhibitor and an HMG Co-A reductase inhibitor with targeted delivery in the gastro-intestinal tract according to any one of the claims 1 to 12 to reduce systemic exposure.

20

14. The use of a pharmaceutical formulation comprising an IBAT inhibitor and an HMG Co-A reductase inhibitor with targeted delivery in the gastro-intestinal tract according to any one of the claims 1 to 12 to enhance the therapeutic effect.

25

15. The use of a pharmaceutical formulation according to any one of the claims 1 to 12 in the treatment of hypercholesterolemia.

30 16. The use of a pharmaceutical formulation according to any one of the claims 1 to 12, in the manufacture of a medicament for the prophylactic or therapeutic treatment of hypercholesterolemia.

WO 02/32429

- 16 -

PCT/CB01/04525

17. A method for prophylactic or therapeutic treatment of a subject suffering from, or susceptible to, hypercholesterolemia, which method comprises administering to the subject a pharmaceutical formulation designed according to any one of claims 1 to 12.
- 5 18. A pharmaceutical formulation for simultaneous, separate or sequential administration in the prophylactic or therapeutic treatment of hypercholesterolemia, which formulation comprises an IBAT inhibitor, an HMG Co-A reductase inhibitor and a bile acid binder.
- 10 19. The pharmaceutical formulation according to claim 18, wherein the IBAT inhibitor is a low permeability drug as defined in claim 10.
- 20 20. The formulation according to claims 18 or 19, wherein the HMG Co-A reductase inhibitor is atorvastatin or a pharmaceutically acceptable salt thereof.
- 15 21. The formulation according to claims 18 or 19, wherein the HMG Co-A reductase inhibitor is (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulphonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof.
- 20 22. The pharmaceutical formulation according to claim 18, wherein the bile acid binder is a resin.
23. The pharmaceutical formulation according to claim 22, wherein the bile acid binder is in a formulation with colon release.
- 25 24. The use of a pharmaceutical formulation according to any one of claims 18 - 23 in the treatment of diarrhoea during therapy comprising an IBAT inhibitor compound.
- 30 25. The use of a pharmaceutical formulation according to any one of the claims 18 to 23, in the manufacture of a medicament for the prophylactic or therapeutic treatment of hypercholesterolemia.

WO 02/32428

PCT/GB01/04525

- 17 -

26. A method for prophylactic or therapeutic treatment of a subject suffering from, or susceptible to, diarrhoea during therapy comprising an IBAT inhibitor compound, which method comprises administering to the subject a pharmaceutical formulation designed according to any one of claims 18 to 23.

5

27. The use of a bile acid binder as prophylaxis or in the treatment of diarrhoea during therapy comprising an IBAT inhibitor and an HMG Co-A reductase inhibitor.